II. REMARKS

A. Status of the Claims

Claims 6, 24, 35, and 37 were amended without prejudice. Support for the amendments to claims 6, 24 and 37 can be found, e.g., on page 18, lines 1-11. Support for the amendments to claim 35 can be found, e.g., on page 15, lines 3-7.

Claims 39-43 were added. Support for new claims 39 to 41 can be found, e.g., on page 15, lines 3-7. Support for new claims 42 and 43, can be found, e.g., on page 17, line 3.

Claims 1-5, 9-12 and 17-23 were previously cancelled without prejudice.

Claims 6-8, 13-16 and 24-43 are now pending.

It is respectfully submitted that no new matter has been added by virtue of the present amendments.

B. Claim rejection under 35 U.S.C. §103

Claims 6-8, 13 and 24-38 were rejected under judicially created doctrine of obviousness-type double patenting over claims 1-19 of the grandparent case (U.S. Patent No. 5,958,459).

Claims 6-8, 13 and 24-38 were rejected under judicially created doctrine of obviousness-type double patenting over claims 1-13 of the parent case (U.S. Patent No. 6,143,322).

Applicants acknowledge the double patenting rejections and submit that filing of the terminal disclaimers will be considered upon indication that claims are otherwise allowable.

C. Claim rejection under 35 U.S.C. §103

Claims 6-8, 13-16 and 24-30 were rejected under 35 U.S.C. §103(a) over Goldie et al. (U.S. 4,844,909). The Examiner stated that "the Applicant's has clearly misread the reference for it does teach all the limitations at issue." The Examiner then took a position that certain features of the present claims are inherent in the compositions of the Goldie reference.

Applicants respectfully disagree. The compositions of the Goldie reference are different from the compositions presently claimed and therefore cannot inherently possess the features recited in the present claims, at the very least for the foregoing reasons.

First, the Goldie reference does not teach or suggest a cured stabilized coating as recited in independent claims 1, 24 and 37.

In response to the Examiner's statement that "the examples of the Goldie reference clearly teach that the dosage form is cured by way of exposure to heat of up to 50 and 60°C," Applicants note that the only example of the Goldie reference that describes a coated formulation is Example 4. The coating in Example 4 was applied after the spheroids were dried, and therefore was not "cured." *See the Goldie reference, column 6, lines 34-36.*

In any event, to further differentiate over the "drying" step of the Goldie reference and advance prosecution, independent claims 6, 24 and 37 have been amended without prejudice to recite that the curing is carried out "for about 24 hours or more ..."

Applicants note that the "traditional" curing (i.e., curing of Eudragit coated formulations ... via a fluid bed at 45°C for 2 hours after application) is different from the curing recited in the present claims and does not stabilize the product as recited in the present claims. *See, e.g., page 17, lines 21-28; see also, U.S. Patent No. 5,286,493, column 11, lines 37-67 (" the short curing*

step recommended in the literature and utilized [in the example] ... did not ... help the stability curing problem").

Second, the Goldie reference also does not teach or suggest "a coating derived from an aqueous dispersion of a hydrophobic polymer" as recited in independent claims 6, 24, 35, and 37, because every time the Goldie reference mentions incorporation of a hydrophobic polymer into the dosage forms described therein, it is always in conjunction with an organic solvent (e.g., methanol 60 % v/v; *see, e.g., the Goldie reference, Example 4*) or a higher aliphatic alcohol.

In response to the Examiner's statement that "the use of water or an organic solvent in the coating process is irrelevant," Applicants submit that the type of the solvent used in the coating matters. *See, e.g., U.S. Patent No. 5,273,760, column 2, lines 25-36:*

> ... to date, attempts to prepare stable controlled release pharmaceutical formulations using aqueous dispersions of hydrophobic polymers have been unsuccessful due to stability problems. In particular, when coating these pharmaceutical forms using aqueous polymeric dispersions to obtain a desired release profile of the active drug(s) over several hours or longer, it is known in the art that the dissolution release profile changes on ageing. It is also known that **this instability problem does not exist when the polymers are applied** from organic solvent solution.

U.S. Patent No. 5,273,760, column 2, lines 25-36 (emphasis added).

Applicants note that the literature (e.g., U.S. Patent No. 5,580,578) states that curing "for about 24 hour or more" as recited in the present claims results in morphological changes to the coating. *See, e.g., U.S. Patent No. 5,580,578, column 19, lines 37-47. ("[a] split-screen SEM of [a coated theophylline bead] ... shows apparent morphological changes to the coating on the surface of the bead," as compared to the coated bead which has not been cured").*

Because the Manual of Patent Examining Procedure mandates in section 2113 that "[t]he structure implied by the process step should be considered when assessing the patentability of the

product-by-process claims over the prior art, especially where the product can only be defined by the process steps by which the product is made ...," Applicants respectfully request that the feature "derived from an aqueous dispersion of a hydrophobic polymer" be considered by the Examiner, especially in view that the "instability problem" addressed by the present claims "does not exist when the polymers are applied from organic solvent solution." *See, e.g., U.S. Patent No. 5,273,760, column 2, lines 25-36 (emphasis added)*

For the foregoing reasons, it is respectfully submitted that the composition of the Goldie reference is different from the composition presently claimed and therefore cannot inherently posses the features recited in the present claims.

In response to the Examiner's statement that "Tables 1-3 of the Goldie reference clearly show that the weight percentage of hydromorphone that is released overlaps with those that are instantly claimed," Applicants note that the dissolution data in Tables 1-3 is for the **uncoated** tablets, and therefore cannot establish that certain features inherent ("is necessarily present") in the **coated** formulations presently claimed.

The Manual of Patent Examining Procedure states that

> To establish inherency, the extrinsic evidence 'must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient.' " *In re Robertson*, 169 F.3d 743, 745, 49 USPQ2d 1949, 1950-51 (Fed. Cir. 1999) (citations omitted).

MPEP Section 2112.

The vivo data for the formulation of Example 1 of the Goldie reference clearly shows that an in-vivo parameter (i.e., Cmax) provided by the Formulation 1 is not and cannot be the same as the presently claims mean maximum plasma concentrations, because the mean plasma

concentrations (e.g., at 1.5 hours, 2.0 hours, 2.5 hours, 3.0 hours, 4.0 hours, 6.0 hours) of the exemplified formulations of the Goldie reference exceed the mean maximum plasma concentrations (Cmax) recited in the present claims. The data therefore cannot establish the inheritancy of the mean Cmax ranges recited in the present claims. *MPEP Section 2112.*

The Goldie reference does not suggest to one skilled in the art to pick the specific mean C_{max} values recited in the present claims out of a theoretically infinite number of possibilities and then formulate the dosage form as recited in the present claims.

Applicants further submit that the Goldie reference does not suggest a dosage form providing an in-vivo release profile as defined by a specific combination of the specific mean C_{max} and T_{max} values recited in the present claims.

With further regard to independent claim 35, Applicants submit that the Goldie reference does not suggest "a barrier coating separating hydromorphone from the controlled-release coating" as recited in this claim.

With further regard to independent claim 37, Applicants submit that the Goldie reference does not describe "at a relative humidity from about 60% to about 100%" as recited in this claim.

In response to the Examiner's statement that "Goldie et al. teaches that dosage form achieving a peak plasma level between 2 and 4 hours are surprisingly interchangeable with dosage forms that achieve peak plasma levels between about 4 and 8 hours after administration," Applicants note that the Goldie reference does not make such an assertion. To the contrary, the Goldie reference differentiates a dosage form that provides a peak plasma level of hydromorphone between 2 and 4 hours, from a dosage form providing a peak plasma level of hydromorphone at from about 4-8 hours, e.g., by stating that:

> ... it is usual in the pharmaceutical art to produce a formulation that gives a peak plasma level of the drug between about 4-8 hours ... The present inventors have surprisingly found that, in the case

> of hydromorphone, a peak plasma level at between 2-4 hours after administration gives at least 12 hours pain relief and, most surprisingly, that the pain relief obtained with such a formulation is greater than that achieved with formulations giving peak plasma levels (of hydromorphone) in the normal period of 1-2 hours after administration."

See Column 2, lines 21-26.

For the foregoing reasons, withdrawal of the rejection is respectfully requested.

III. CONCLUSION

An early and favorable action on the merits is earnestly solicited. The Examiner is specifically authorized to contact the undersigned by telephone in the event a telephone interview would advance the prosecution of the application.

Respectfully submitted,
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